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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b)

Attorney Docket No. B00-001-3

First Named Inventor or Application Identifier Ames et al.

Title Primary N-hydroxylamines

Express Mail Label No. EV324953194US

EV324953194US

ADDRESS TO:
Mail Stop Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. X *Fee Transmittal Form
(Submit an original, and a duplicate for fee processing)

2. X Applicant claims small entity status (see 37 CFR 1.27)

3. X Specification (Total Pages 59)
(preferred arrangement set forth below)
- Descriptive Title of the Invention
- Cross References to Related Applications
- Statement Regarding Fed sponsored R & D
- Reference to sequence listing, a table, or a computer program listing appendix
- Background of the Invention
- Brief Summary of the Invention
- Brief Description of the Drawings (if filed)
- Detailed Description
- Claims
- Abstract of the Disclosure

4. _ Drawings(s) (35 USC 113) (Total Sheets _____)

5. X Oath or Declaration (Total Pages 1)

a. ___ Newly Executed (Original or Copy)

b. X Copy from a Prior Application (37 CFR 1.63(d))
(for Continuation/Divisional with Box 17 completed)

i. ___ DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).

6. ____ Application Data Sheet. See 37 CFR 1.76

7. ___ CD-ROM or CD-R in duplicate, large table or Computer Program (Appendix)

8. Nucleotide and/or Amino Acid Sequence Submission

(if applicable, all necessary)

a. ___ Computer Readable Form (CRF)
b. ___ Specification Sequence Lising on: i. ___ CD-ROM or CD-R (2 copies); or ii. ____ paper
c. ___ Statement verifying identity of above copies
d. ___ Request to use CRF from another application

ACCOMPANYING APPLICATION PARTS

9. X Assignment Papers (cover sheet & documents(s))

10. X 37 CFR 3.73(b) Statement (where there is an assignee)

X Power of Attorney

11. _ English Translation Document (if applicable)

12. X a. Information Disclosure Statement (IDS)/PTO-1449

_ b. Copies of IDS Citations

13. _ Preliminary Amendment

14. X Return Receipt Postcard (MPEP 503) (Should be specifically itemized)

15. _ Certified Copy of Priority Document(s) (if foreign priority is claimed)

16. X Other: Transmittal letter and Remington ref. (3p)

17. **Priority**

This application claims priority to prior application No: 10/038,135, filed 10/20/01, having the same title and inventors

Prior application information: Examiner Jones, D. Group Art Unit 1614

The entire disclosure of the prior application, from which an oath or declaration is supplied under 5b, is considered a part of the disclosure of the accompanying application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

18. **Correspondence Address**

X Customer Number or Bar Code Label **23379**
(Insert Customer No. or Attach Bar Code Label here)

or

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Signature: Date: November 13, 2003

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FEE TRANSMITTAL EFFECTIVE OCTOBER 1, 2003

Fees are subject to annual revision

TOTAL AMOUNT OF PAYMENT ($) $758.00

Complete if Known:

Application No. Not yet assigned
Filing Date Herewith
First Named Inventor Ames et al.
Group Art Unit Not yet assigned
Examiner Name Not yet assigned
Attorney Docket No. B00-001-3

METHOD OF PAYMENT (check one)

1. [X] The Commissioner is hereby authorized to charge indicated fees to:

   [X] Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17 and credit any over payments to:

   [X] Applicant claims small entity status. See 37 CFR 1.27

   Deposit Account Number 19-0750
   Deposit Account Name Science & Technology Law Group

2. X Payment Enclosed
   X Check
   ____ Money Order
   ____ Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility application filing fee	385.
1002	340	2002	175	Design application filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional application filing fee	

SUBTOTAL (1) $ 385.00

2. CLAIMS

			Extra		Fee from below		Fee Paid
Total Claims	57	– 20 =	37	X	9.00	=	333.00
Independent Claims	1	– 3 =	0	X		=	0
Multiple Dependent Claims			0	X		=	0

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1202	18	2202	9	Claims in excess of twenty	333.00
1201	86	2201	43	Independent claims in excess of 3	0
1203	290	2203	145	Multiple dependent claim	0
1204	86	2204	43	Reissue independent claims over original patent	0
1205	18	2205	9	Reissue claims in excess of 20 and over original patent	0

SUBTOTAL (2) $ 333.00

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for ex parte reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for response within first month	
1252	420	2252	210	Extension for response within second month	
1253	950	2253	475	Extension for response within third month	
1254	1,480	2254	740	Extension for response within fourth month	
1255	2,010	2255	1,005	Extension for response within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive unavoidably abandoned application	
1453	1,330	2453	665	Petition to revive unintentionally abandoned application	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	40.00
1809	770	2809	385	For filing a submission after final rejection (see 37 CFR 1.129(a))	
2810	770	1810	385	For each additional invention to be examined (see 37 CFR 1.129(a))	
Other fee (specify)					
Other fee (specify)					

SUBTOTAL (3) $ 40.00

*Reduced by Basic Filing Fee Paid

SUBMITTED BY:

Typed or Printed Name: Richard Aron Osman

Signature _____ **Date** November 13, 2003

Reg. Number 36,627 **Deposit Account User ID** _____ (complete if applicable)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Ames et al.	Group Art Unit: Not yet assigned
Serial No. Not yet assigned	Examiner: Not yet assigned
Filed: Herewith	Attorney Docket No. B00-001-3
For: *Primary N-hydroxylamines*	Date: November 13, 2003

This application is a continuation of US Serial No 10/038,135, filed 10/20/01, which is a continuation of US Serial No 09/429,412, filed 10/28/99, now US Pat No 6,455,589.

TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

This application is a continuation of Serial No. 10/038,135, filed October 20, 2001 which is a continuation of Serial No. 09/429,412 filed October 28, 1999, now US Pat No. 6,455,589, both having the same title and inventors. The enclosed Specification is identical to that of prior application 10/038,135, except for minor formatting changes, a cross-reference to the parent applications, incorporation of a definition of prodrug from Remington's Pharmaceutical Sciences, 17th edition, 1985, Mack Publishing Company, Easton, Pa. (the copyright and excerpted page 1654 are attached) which was expressly incorporated by reference in the parent application, and a new set of claims. As noted in the Specification, a corresponding nitrone means a nitrone condensate of the hydroxylamine and hence, having the same nitrogen bound R group, i.e. the condensation product of the primary N-hyroxyl amine with an aldehyde. These changes introduce no new matter.

The new claims are identical to claims issued in US Pat No. 6,455,589, except that the recitations of the redundant "R", "solid", and "substantially free ..." are canceled, and the recitation of a corresponding nitrone prodrug is added.

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP

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$$\text{Resin}^+\text{-Drug}^- + X^- \longrightarrow \text{Resin}^+\text{-}X^- + \text{Drug}^-$$

$$\text{or Resin}^-\text{-Drug}^+ + Y^+ \longrightarrow \text{Resin}^-\text{-}Y^+ + \text{Drug}^+$$

where X^- and Y^+ are ions in the GI tract.

Fig 92-10.

exchange cationic drugs such as those with an amine functionality. Examples of some of these drugs are amphetamine, phenyl *t*-butylamine (phentermine), phenyltoloxamine, and hydrocodone, as shown in Table VI.

Table VI—Ion Exchang Products

Product	Active ingredient(s)	Manufacturer
Biphetamine capsules	amphetamine, dextroamphetamine	Pennwalt
Tussionex capsules, tablets, suspension	hydrocodone, phenyltoloxamine	Pennwalt
Ionamin capsules	phentermine	Pennwalt

Prodrugs

A prodrug is a compound formed by chemical modification of a biologically active compound which will liberate the active compound *in vivo* by enzymatic or hydrolytic cleavage. The primary purpose of employing a prodrug for oral administration is to increase intestinal absorption or to reduce local side effects, such as GI irritation by aspirin. On this basis, one does not generally classify a prodrug as a sustained-release dosage form. However, the ability to bioreversibly modify the physicochemical properties of a drug allows better intestinal transport properties and hence influences the drug blood level versus time profile. Thus, prodrugs can be used to increase the strategies for sustained release and, in a limited sense, can be sustaining in their own right.

As an example of the use of a prodrug as a sustaining mechanism, consider a water-soluble drug which is modified to a water-insoluble prodrug. The prodrug will have a slower dissolution rate in aqueous fluid than the parent drug and thus the appearance of the parent drug in plasma will be slowed. This is observed with theophylline and its prodrug 7,7′-succinylditheophylline. Alternatively, a water-soluble prodrug of a water-insoluble parent drug can be made to be a substrate for enzymes in the brush border region of the microvilli. The water-soluble prodrug complexes with the enzyme just prior to reaching the membrane surface, is metabolized, and its membrane/water partition coefficient increases. The result is an increase in the blood level of the drug. See Chapter 27.

Parenteral Dosage Forms

The most common types of dosage forms used for parenteral sustained-release drug therapy are intramuscular (IM) injections, implants for subcutaneous tissues and various body cavities, and transdermal devices. Due to physiological and anatomical constraints, many of the other parenteral routes of administration, eg, intravenous, intraarterial, intrathecal, and intraperitoneal, are not as useful in this regard. The application of the former three types of dosage forms to sustained-release drug delivery will be discussed in this section. The final section is devoted to other parenteral dosage forms being developed for targeted drug delivery.

Intramuscular Injections

Complex Formation

The formation of a dissociable complex of a drug with a macromolecule is the same physicochemical phenomenon which occurs when a drug binds to a plasma protein. In this sense, the drug–macromolecule complex can serve as a reservoir at the site of injection for sustained drug release to the surrounding tissues. The macromolecules used are either biological polymers such as antibodies and proteins, or synthetic polymers such as polyvinylpyrrolidone or polyethylene glycol. Drug release from the polymer is governed by the degree of association, as given by the following equation,

$$D + P \underset{}{\overset{K_a}{\rightleftharpoons}} DP \qquad (33)$$

where D, P, and DP represent drug, polymer, and complex, respectively, and K_a is the apparent association constant. Only that fraction of the drug which is free, f, can be absorbed;

$$f = \frac{(D)}{(DP) + (D)} = \frac{1}{1 + K_a(P)} \qquad (34)$$

where (D), (P), and (DP) are equilibrium concentrations of drug, polymer, and complex, respectively. If $K_a(P)$ is much greater than 1, Eq 34 reduces to,

$$f = 1/[K_a(P)] \qquad (35)$$

The rate of absorption of the drug, $d(C)/dt$, is therefore described by,

$$d(C)/dt = k_a f(D_t) = [k_a(D_t)]/[K_a(P)] \qquad (36)$$

where (D_t) is the total drug concentration at the absorption site, ie, $(DP) + (D)$, and k_a is the absorption rate constant. It can be seen from Eq 36 that the rate of absorption can be controlled effectively by the type and concentration of polymer used, assuming that dissociation is instantaneous compared to absorption.

Complexes can also be formed between drugs and small molecules rather than macromolecules. The motive behind formation of a drug–small molecule complex is to alter the physicochemical properties of the drug and thus affect changes in its biological disposition. Unlike macromolecular complexes, drug–small molecule complexes are capable of being absorbed. They usually have very small association constants, however, which means that most of the drug is free. This nullifies any advantage gained from alteration of properties upon complexation. If the drug molecule is large relative to the complexing agent, the association constant will be greater and the complex more stable. This is the approach that has been taken commercially with polypeptide hormones, such as adrenocorticotropic hormone (ACTH) and insulin, and with vitamins such as cyanocobalamin (vitamin B_{12}). The ACTH product, Acthar Gel HP (*Armour*) consists of an ACTH–zinc tannate complex suspended in a gelatin solution. Tannic acid acts as the complexing agent and gelatin inhibits protein binding of ACTH. An analogous product is Depinar (*Armour*), which is a cyanocobalamin–zinc tannate complex suspended in sesame oil. With both of these products, the sustained effect is due to, among other things, a reduction in solubility of the parent drug upon complexation, and not dissociation. In this respect they are much like aqueous suspensions.

Aqueous Suspensions

The rate-limiting step in drug release from an aqueous suspension is dissolution, as given by the Noyes-Whitney equation (Eq 28). The parameters influencing dissolution